

APPENDIX C

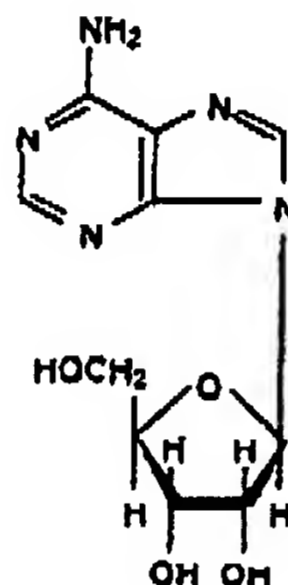
ADENOSCAN
(adenosine injection)

FOR INTRAVENOUS INFUSION ONLY

Revised. July 2005

DESCRIPTION

Adenosine is an endogenous nucleoside occurring in all cells of the body. It is chemically 6-amino-9-beta-D-ribofuranosyl-9-H-purine and has the following structural formula:



C₁₀H₁₃N₅O₄

267.24

Adenosine is a white crystalline powder. It is soluble in water and practically insoluble in alcohol. Solubility increases by warming and lowering the pH of the solution.

Each Adenoscan vial contains a sterile, non-pyrogenic solution of adenosine 3 mg/mL and sodium chloride 9 mg/mL in Water for Injection, q.s. The pH of the solution is between 4.5 and 7.5.

CLINICAL PHARMACOLOGY

Mechanism of Action

Adenosine is a potent vasodilator in most vascular beds, except in renal afferent arterioles and hepatic veins where it produces vasoconstriction. Adenosine is thought to exert its pharmacological effects through activation of purine receptors (cell-surface A₁ and A₂ adenosine receptors). Although the exact mechanism by which adenosine receptor activation relaxes vascular smooth muscle is not known, there is evidence to support both inhibition of the slow inward calcium current reducing calcium uptake, and activation of adenylate cyclase through A₂ receptors in smooth muscle cells. Adenosine may also lessen vascular tone by modulating sympathetic neurotransmission. The intracellular uptake of adenosine is mediated by a specific transmembrane nucleoside transport system. Once inside the cell, adenosine is rapidly

36 phosphorylated by adenosine kinase to adenosine monophosphate, or
37 deaminated by adenosine deaminase to inosine. These intracellular metabolites
38 of adenosine are not vasoactive.

39 Myocardial uptake of thallium-201 is directly proportional to coronary blood flow.
40 Since Adenoscan significantly increases blood flow in normal coronary arteries
41 with little or no increase in stenotic arteries, Adenoscan causes relatively less
42 thallium-201 uptake in vascular territories supplied by stenotic coronary arteries
43 i.e., a greater difference is seen after Adenoscan between areas served by
44 normal and areas served by stenotic vessels than is seen prior to Adenoscan.

45 **Hemodynamics**

46 Adenosine produces a direct negative chronotropic, dromotropic and inotropic
47 effect on the heart, presumably due to A₁-receptor agonism, and produces
48 peripheral vasodilation, presumably due to A₂-receptor agonism. The net effect
49 of Adenoscan in humans is typically a mild to moderate reduction in systolic,
50 diastolic and mean arterial blood pressure associated with a reflex increase in
51 heart rate. Rarely, significant hypotension and tachycardia have been observed.

52 **Pharmacokinetics**

53 Intravenously administered adenosine is rapidly cleared from the circulation via
54 cellular uptake, primarily by erythrocytes and vascular endothelial cells. This
55 process involves a specific transmembrane nucleoside carrier system that is
56 reversible, nonconcentrative, and bidirectionally symmetrical. Intracellular
57 adenosine is rapidly metabolized either via phosphorylation to adenosine
58 monophosphate by adenosine kinase, or via deamination to inosine by
59 adenosine deaminase in the cytosol. Since adenosine kinase has a lower K_m
60 and V_{max} than adenosine deaminase, deamination plays a significant role only
61 when cytosolic adenosine saturates the phosphorylation pathway. Inosine
62 formed by deamination of adenosine can leave the cell intact or can be
63 degraded to hypoxanthine, xanthine, and ultimately uric acid. Adenosine
64 monophosphate formed by phosphorylation of adenosine is incorporated into
65 the high-energy phosphate pool. While extracellular adenosine is primarily
66 cleared by cellular uptake with a half-life of less than 10 seconds in whole
67 blood, excessive amounts may be deaminated by an ecto-form of adenosine
68 deaminase. As Adenoscan requires no hepatic or renal function for its activation
69 or inactivation, hepatic and renal failure would not be expected to alter its
70 effectiveness or tolerability.

71 **Clinical Trials**

72 In two crossover comparative studies involving 319 subjects who could exercise
73 (including 106 healthy volunteers and 213 patients with known or suspected
74 coronary disease), Adenoscan and exercise thallium images were compared by
75 blinded observers. The images were concordant for the presence of perfusion
76 defects in 85.5% of cases by global analysis (patient by patient) and up to 93%
77 of cases based on vascular territories. In these two studies, 193 patients also

78 had recent coronary arteriography for comparison (healthy volunteers were not
79 catheterized). The sensitivity (true positive Adenoscan divided by the number of
80 patients with positive (abnormal) angiography) for detecting angiographically
81 significant disease ($\geq 50\%$ reduction in the luminal diameter of at least one
82 vessel) was 64% for Adenoscan and 64% for exercise testing, while the
83 specificity (true negative divided by the number of patients with negative
84 angiograms) was 54% for Adenoscan and 65% for exercise testing. The 95%
85 confidence limits for Adenoscan sensitivity were 56% to 78% and for specificity
86 were 37% to 71%.

87 Intracoronary Doppler flow catheter studies have demonstrated that a dose of
88 intravenous Adenoscan of 140 mcg/kg/min produces maximum coronary
89 hyperemia (relative to intracoronary papaverine) in approximately 95% of cases
90 within two to three minutes of the onset of infusion. Coronary blood flow velocity
91 returns to basal levels within one to two minutes of discontinuing the
92 Adenoscan infusion.

93 **INDICATIONS AND USAGE**

94 Intravenous Adenoscan is indicated as an adjunct to thallium-201 myocardial
95 perfusion scintigraphy in patients unable to exercise adequately (See
96 **WARNINGS**).

97

98 **CONTRAINDICATIONS**

99 Intravenous Adenoscan (adenosine injection) should not be administered to
100 individuals with.

- 101 1. Second- or third-degree AV block (except in patients with a functioning
102 artificial pacemaker).
- 103 2. Sinus node disease, such as sick sinus syndrome or symptomatic
104 bradycardia (except in patients with a functioning artificial pacemaker).
- 105 3. Known or suspected bronchoconstrictive or bronchospastic lung disease
106 (e.g., asthma).
- 107 4. Known hypersensitivity to adenosine.

108 **WARNINGS**

109 **Fatal Cardiac Arrest, Life Threatening Ventricular Arrhythmias, and** 110 **Myocardial Infarction**

111 Fatal cardiac arrest, sustained ventricular tachycardia (requiring resuscitation),
112 and nonfatal myocardial infarction have been reported coincident with
113 Adenoscan infusion. Patients with unstable angina may be at greater risk.
114 Appropriate resuscitative measures should be available.
115

116 **Sinoatrial and Atrioventricular Nodal Block**

117 Adenoscan (adenosine injection) exerts a direct depressant effect on the SA
118 and AV nodes and has the potential to cause first-, second- or third-degree AV
119 block, or sinus bradycardia. Approximately 6.3% of patients develop AV block

120 with Adenoscan, including first-degree (2.9%), second-degree (2.6%), and third-
121 degree (0.8%) heart block. All episodes of AV block have been asymptomatic,
122 transient, and did not require intervention. Adenoscan can cause sinus
123 bradycardia. Adenoscan should be used with caution in patients with pre-
124 existing first-degree AV block or bundle branch block and should be avoided in
125 patients with high-grade AV block or sinus node dysfunction (except in patients
126 with a functioning artificial pacemaker). Adenoscan should be discontinued in
127 any patient who develops persistent or symptomatic high-grade AV block. Sinus
128 pause has been rarely observed with adenosine infusions.

129 **Hypotension**

130 Adenoscan (adenosine injection) is a potent peripheral vasodilator and can
131 cause significant hypotension. Patients with an intact baroreceptor reflex
132 mechanism are able to maintain blood pressure and tissue perfusion in
133 response to Adenoscan by increasing heart rate and cardiac output. However,
134 Adenoscan should be used with caution in patients with autonomic dysfunction,
135 stenotic valvular heart disease, pericarditis or pericardial effusions, stenotic
136 carotid artery disease with cerebrovascular insufficiency, or uncorrected
137 hypovolemia, due to the risk of hypotensive complications in these patients.
138 Adenoscan should be discontinued in any patient who develops persistent or
139 symptomatic hypotension

140 **Hypertension**

141 Increases in systolic and diastolic pressure have been observed (as great as
142 140 mm Hg systolic in one case) concomitant with Adenoscan infusion; most
143 increases resolved spontaneously within several minutes, but in some cases,
144 hypertension lasted for several hours.

145 **Bronchoconstriction**

146 Adenoscan (adenosine injection) is a respiratory stimulant (probably through
147 activation of carotid body chemoreceptors) and intravenous administration in
148 man has been shown to increase minute ventilation (V_e) and reduce arterial
149 PCO_2 causing respiratory alkalosis. Approximately 28% of patients experience
150 breathlessness (dyspnea) or an urge to breathe deeply with Adenoscan. These
151 respiratory complaints are transient and only rarely require intervention.

152 Adenosine administered by inhalation has been reported to cause
153 bronchoconstriction in asthmatic patients, presumably due to mast cell
154 degranulation and histamine release. These effects have not been observed in
155 normal subjects. Adenoscan has been administered to a limited number of
156 patients with asthma and mild to moderate exacerbation of their symptoms has
157 been reported. Respiratory compromise has occurred during adenosine infusion
158 in patients with obstructive pulmonary disease. Adenoscan should be used with
159 caution in patients with obstructive lung disease not associated with
160 bronchoconstriction (e.g., emphysema, bronchitis, etc.) and should be avoided
161 in patients with bronchoconstriction and bronchospasm (e.g., asthma)

162 Adenoscan should be discontinued in any patient who develops severe
163 respiratory difficulties.

164 **PRECAUTIONS**

165 **Drug Interactions**

166 Intravenous Adenoscan (adenosine injection) has been given with other
167 cardioactive drugs (such as beta adrenergic blocking agents, cardiac
168 glycosides, and calcium channel blockers) without apparent adverse
169 interactions, but its effectiveness with these agents has not been systematically
170 evaluated. Because of the potential for additive or synergistic depressant
171 effects on the SA and AV nodes, however, Adenoscan should be used with
172 caution in the presence of these agents.

173 The vasoactive effects of Adenoscan are inhibited by adenosine receptor
174 antagonists, such as methylxanthines (e.g., caffeine and theophylline). The
175 safety and efficacy of Adenoscan in the presence of these agents has not been
176 systematically evaluated.

177 The vasoactive effects of Adenoscan are potentiated by nucleoside transport
178 inhibitors, such as dipyridamole. The safety and efficacy of Adenoscan in the
179 presence of dipyridamole has not been systematically evaluated.

180 Whenever possible, drugs that might inhibit or augment the effects of adenosine
181 should be withheld for at least five half-lives prior to the use of Adenoscan.

182 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

183 Studies in animals have not been performed to evaluate the carcinogenic
184 potential of Adenoscan (adenosine injection). Adenosine was negative for
185 genotoxic potential in the Salmonella (Ames Test) and Mammalian Microsome
186 Assay.

187 Adenosine, however, like other nucleosides at millimolar concentrations present
188 for several doubling times of cells in culture, is known to produce a variety of
189 chromosomal alterations.

190 Fertility studies in animals have not been conducted with adenosine.

191 **Pregnancy Category C**

192 Animal reproduction studies have not been conducted with adenosine; nor have
193 studies been performed in pregnant women. Because it is not known whether
194 Adenoscan can cause fetal harm when administered to pregnant women,
195 Adenoscan should be used during pregnancy only if clearly needed.

196
197 **Pediatric Use**

198 The safety and effectiveness of Adenoscan in patients less than 18 years of
199 age have not been established.

200

201

Geriatric Use

202

Clinical studies of Adenoscan did not include sufficient numbers of subjects

203

aged younger than 65 years to determine whether they respond differently

204

Other reported experience has not revealed clinically relevant differences of the response of elderly in comparison to younger patients. Greater sensitivity of some older individuals, however, cannot be ruled out.

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ADVERSE REACTIONS

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The following reactions with an incidence of at least 1% were reported with intravenous Adenoscan among 1421 patients enrolled in controlled and uncontrolled U.S. clinical trials. Despite the short half-life of adenosine, 10.6% of the side effects occurred not with the infusion of Adenoscan but several hours after the infusion terminated. Also, 8.4% of the side effects that began coincident with the infusion persisted for up to 24 hours after the infusion was complete. In many cases, it is not possible to know whether these late adverse events are the result of Adenoscan infusion.

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| | |
|-----------------------------------|-----|
| Flushing | 44% |
| Chest discomfort | 40% |
| Dyspnea or urge to breathe deeply | 28% |
| Headache | 18% |
| Throat, neck or jaw discomfort | 15% |
| Gastrointestinal discomfort | 13% |
| Lightheadedness/dizziness | 12% |
| Upper extremity discomfort | 4% |
| ST segment depression | 3% |
| First-degree AV block | 3% |
| Second-degree AV block | 3% |
| Paresthesia | 2% |
| Hypotension | 2% |
| Nervousness | 2% |
| Arrhythmias | 1% |

218

Adverse experiences of any severity reported in less than 1% of patients include:

219

220

Body as a Whole

221

Back discomfort; lower extremity discomfort; weakness

222

223

224

Cardiovascular System

225

Nonfatal myocardial infarction; life-threatening ventricular arrhythmia; third-degree AV block; bradycardia; palpitation; sinus exit block; sinus pause,

226

227 sweating; T-wave changes; hypertension (systolic blood pressure > 200 mm
228 Hg)

229

230 **Central Nervous System**

231 Drowsiness; emotional instability; tremors

232

233 **Genital/Urinary System**

234 Vaginal pressure; urgency

235

236 **Respiratory System**

237 Cough

238

239 **Special Senses**

240 Blurred vision, dry mouth; ear discomfort; metallic taste; nasal congestion;
241 scotomas; tongue discomfort

242

243 **Post Marketing Experience (see WARNINGS)**

244 The following adverse events have been reported from marketing experience
245 with Adenoscan. Because these events are reported voluntarily from a
246 population of uncertain size, are associated with concomitant diseases and
247 multiple drug therapies and surgical procedures, it is not always possible to
248 reliably estimate their frequency or establish a causal relationship to drug
249 exposure. Decisions to include these events in labeling are typically based on
250 one or more of the following factors: (1) seriousness of the event, (2) frequency
251 of the reporting, (3) strength of causal connection to the drug, or a combination
252 of these factors

253

254 **Body as a Whole**

255 Injection site reaction

256

257 **Central Nervous System**

258 Seizure activity, including tonic clonic (grand mal) seizures, and loss of
259 consciousness

260

261 **Digestive**

262 Nausea and vomiting

263

264 **Respiratory**

265 Respiratory arrest

266

267 **OVERDOSAGE**

268 The half-life of adenosine is less than 10 seconds and side effects of
269 Adenoscan (when they occur) usually resolve quickly when the infusion is
270 discontinued, although delayed or persistent effects have been observed.
271 Methylxanthines, such as caffeine and theophylline, are competitive adenosine
272 receptor antagonists and theophylline has been used to effectively terminate

273 persistent side effects. In controlled U.S. clinical trials, theophylline (50-125 mg
274 slow intravenous injection) was needed to abort Adenoscan side effects in less
275 than 2% of patients.

276

277 **DOSAGE AND ADMINISTRATION**

278 For intravenous infusion only.

279 Adenoscan should be given as a continuous peripheral intravenous infusion.

280 The recommended intravenous dose for adults is 140 mcg/kg/min infused for
281 six minutes (total dose of 0.84 mg/kg).

282

283 The required dose of thallium-201 should be injected at the midpoint of the
284 Adenoscan infusion (i.e., after the first three minutes of Adenoscan). Thallium-
285 201 is physically compatible with Adenoscan and may be injected directly into
286 the Adenoscan infusion set

287

288 The injection should be as close to the venous access as possible to prevent
289 and inadvertent increase in the dose of Adenoscan (the contents of the IV
290 tubing) being administered.

291

292 There are no data on the safety or efficacy of alternative Adenoscan infusion
293 protocols.

294

295 The safety and efficacy of Adenoscan administered by the intracoronary route
296 have not been established.

297

298 The following Adenoscan infusion nomogram may be used to determine the
299 appropriate infusion rate corrected for total body weight:

300

| Patient Weight | | Infusion Rate |
|----------------|-----|---------------|
| kg | lbs | mL/min |
| 45 | 99 | 2.1 |
| 50 | 110 | 2.3 |
| 55 | 121 | 2.6 |
| 60 | 132 | 2.8 |
| 65 | 143 | 3.0 |
| 70 | 154 | 3.3 |
| 75 | 165 | 3.5 |
| 80 | 176 | 3.8 |
| 85 | 187 | 4.0 |
| 90 | 198 | 4.2 |

301

302

303

304 This nomogram was derived from the following general formula:

$$\frac{0.140 \text{ (mg/kg/min)} \times \text{total body weight (kg)}}{\text{Adenoscan concentration (3 mg/mL)}} = \text{Infusion rate (mL/min)}$$

305

306 **Note:** Parenteral drug products should be inspected visually for particulate
307 matter and discoloration prior to administration.

308 **HOW SUPPLIED**

309 Adenoscan (adenosine injection) is supplied as 20 mL and 30 mL vials of
310 sterile, nonpyrogenic solution in normal saline.

311 NDC 0469-0871-20 Product Code 87120
312 60 mg/20 mL (3 mg/mL) in a 20 mL single-dose, flip-top glass vial, packaged
313 individually and in packages of ten.

314
315 NDC 0469-0871-30 Product Code 87130
316 90 mg/30 mL (3 mg/mL) in a 30 mL single-dose, flip-top glass vial, packaged
317 individually and in packages of ten.

318
319 Store at controlled room temperature 15°-30°C (59°-86°F)

320
321 Do not refrigerate as crystallization may occur. If crystallization has occurred,
322 dissolve crystals by warming to room temperature. The solution must be clear
323 at the time of use.

324 Contains no preservative. Discard unused portion.

325 **Rx only**

326 **Marketed by:**
327 Astellas Pharma US, Inc.
328 Deerfield, IL 60015-2548

329
330 **Manufactured by:**
331 Hospira, Inc.
332 Lake Forest, IL 60045 USA

333
334 Revised: July 2005
335



McDonnell Boehnen Hulbert & Berghoff
Law Offices

Fax transmittal

To Examiner Crane
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with cover 11

Date September 14, 2006
From A. Blair Hughes
Direct 312 913 2123
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C/M

Re U.S. Patent Application Serial No. 10/629,368
MBHB Case No. 02-479-C

Dear Examiner Crane:

Attached hereto is a copy of Appendix C which accompanied Applicant's Reply to the May 31, 2006 Office Action for the above-identified patent application.

Very truly yours,

A handwritten signature in black ink, appearing to read "A. Blair Hughes".

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